REMARKS

Status of the Claims.

Claims 1-4, 6-10, 20-29, 31 and 32 are pending with entry of this amendment, claims 5, 11-19, and 30 having been cancelled and claim 32 having been added. Claims 1 and 20 are amended herein. These amendments introduce no new matter. Support is replete throughout the specification and in the claims as originally filed.

35 U.S.C. §112, First Paragraph.

A) Make and use enablement.

The rejection of claims 1-4, 6-10, 20-29, and 31 under 35 U.S.C. §112, first paragraph was maintained. The Examiner alleged that the specification is not enabling for a method of increasing the efficacy of a gastric H+/K+-ATPase inhibitor (PPI) in a human in need of a PPI by administering an effective amount (e.g., 0.1-10 mg/kg/hr) of a pentagastrin, a gastrin, or a gastrin analogue in conjunction with the PPI" . . . "because the specification discloses cursory conclusions without data supporting the findings . . . ". Applicants traverse.

The Examiner is respectfully reminded that M.P.E.P. §2164.01(c) expressly states:

> **If a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated,** 35 U.S.C. 112 **is satisfied.** *In re Johnson*, 282 F.2d 370, 373, 127 USPQ 216, 219 (CCPA 1960); *In re Hitchings*, 342 F.2d 80, 87, 144 USPQ 637, 643 (CCPA 1965). See also *In re Brana,* 51 F.2d 1560, 1566, 34 USPQ2d 1437, 1441 (Fed. Cir. 1993).
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> For example, **it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation**. If one skilled in the art**, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph**. The applicant need not demonstrate that the invention is completely safe. See also MPEP § 2107.01 and § 2107.03. **[emphasis added]**

In the instant case, the claims are directed to:

> 1. A method of increasing the efficacy of a gastric H+/K+-ATPase pump inhibitor (PPI) in a human in need of a PPI, said method comprising:
> administering to said human an effective amount of one or more agents selected from the group consisting of a pentagastrin, a gastrin, and a gastrin analogue, in conjunction with said gastric proton pump inhibitor whereby the efficiency of said gastric proton pump inhibitor is increased.

The claims simply require administration of a PPI in conjunction with a pentagastrin or a gastrin. In the instant case, proton pump inhibitors **(PPIs) are well known to those of skill in the art, are routinely administered to humans** (*see, e.g.,* Omeprazole (brand names: Losec®, Prilosec®), Lansoprazole (brand names: Prevacid®, Zoton®, Inhibitol®), Esomeprazole (brand names: Nexium®), Pantoprazole (brand names: Protonix®, Somac®, Pantoloc®), and Rabeprazole (brand names: Rabecid®, Aciphex®, Pariet®). Similarly, **both gastrin and pentagastrin have been administered to various animals and humans**, *e.g.* as a model system (*see, e.g.*, Example 1) and **tolerances of humans for gastrin and pentagastrin are well known to those of skill in the art**.

The art thus recognizes standard modes of administration of both PPIs and gastrin/pentagastrin. Routine optimization of dosages is readily accomplished by one of skill in the art without undue experimentation. Accordingly, per M.P.E.P. §2164.01(c) 35 U.S.C. §112, first paragraph, is satisfied.

B) Operability.

The Examiner appears to allege, as the basis for the rejection under 35 U.S.C. §112, first paragraph, that Applicants have provided no working examples and thereby failed to establish the operability of the claimed invention. Since both PPIs and pentagastrin/gastrin have been administered to humans (*see, e.g.,* Example 1), therapeutic dosages for PPIs are well known, and tolerances of humans to gastrin or pentagastrin are well known, the administration of both agents in conjunction with each other is readily accomplished by one of skill in the art and dose optimization requires, at most, routine experimentation. **The Examiner's rejection really goes to the alleged operability of the invention (in effect the Examiner asserts that Applicants haven't proven the invention/method works as claimed)**. Applicants traverse.

The Examiner is reminded that rejection based on the allegation that an invention is "not useful or operative should properly be made both under 35 U.S.C. §112, first paragraph, **and** 35 U.S.C. §101(a) (*see* M.P.E.P. §2164.07 I.A.). The Examiner is further reminded that:

> Compliance with the enablement requirement of 35 U.S.C. §112, first paragraph, **does not turn on whether an example is disclosed**.
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> * * *
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> **An applicant need not have actually reduced the invention to practice prior to filing**. (M.P.E.P. §2164.02).
>
> When the examiner concludes that an application is describing an invention that is nonuseful, inoperative, or contradicts known scientific principles, **the burden is on the examiner to provide a reasonable basis** to support this conclusion. (M.P.E.P §2164.07 I.B.)

In the instant case, Applicants have provided **objective evidence** that pentagastrin increases the efficacy of a typical PPI. As explained in the previous response, Barda *et al.* (2004) *Supplement to Gastroenterology*, 12(4): Suppl. 2, Abstract M1439 states:

> These data indicate that **prestimulation of gastric proton pumps with oral PG [pentagastrin] enhances the inhibitory effect of omeprazole** [a PPI] on acid secretion. This effect is mediated by a local effect of PG. **Co-administraton of PG and omeprazole may be used clinically to potentiate the therapeutic effect of omeprazole**. [emphasis added]

In response, the Examiner alleged that:

1) Barda *et al.* (2004) is a post filing reference, the content of the reference cannot be used as the omitted description for the specification at the time of filing of the instant application; and

2) [T]he claimed method is directed to a method of increasing the efficacy of a PPI in a human subject in need of PPI treatment which is not directly correlated to the rate model indicated in Barda *et al.*

It is well accepted law, however, that a post-filing reference can be used to support the operability of a claimed method. For example, in *In re Brana*, a declaration filed during prosecution was deemed sufficient to meet the Applicants burden:

> [A]pplicants provided through Dr. Kluge's declaration[19] test results showing that several compounds within the scope of the claims exhibited significant antitumor activity against the L1210 standard tumor model *in vivo*. ***Such evidence alone should have been sufficient to satisfy applicants' burden***. [emphasis added] (*In re Brana, 34 USPQ2d 11436, 1441-1442*)

Barda *et al.* clearly and unequivocally established that prestimulation of gastric proton pumps with oral pentagastrin **enhances the inhibitory effect of omeprazole (a PPI)**. It is noted that pentagastrin (essentially a truncated gastrin) and gastrin operate by the same mechanism. Similarly PPIs also act by essentially the same mechanism. Thus, the pentagastrin/omeprazole model is a good model for any gastrin/pentagastrin and PPI combination.

Similarly the rat model discussed in Barda *et al.* is a standard model for the gastric secretion system and is believed to be predictive for efficacy in humans.

The Examiner has failed to provide any objective evidence to refute Barda *et al.* Specifically the Examiner has offered no objective basis to establish why the pentagastrin/omeprazole combination is not predictive for the combination of gastrin or pentagastrin and any other PPI. Similarly the Examiner has offered no objective basis to establish why the rat model is not a good model for behavior of these agents in humans. Accordingly the Examiner has failed to refute Applicants' evidence and the rejection under 35 U.S.C. §112, first paragraph/35 U.S.C. §101(a) should be withdrawn.

In this regard, the Examiner is also reminded that the Federal Circuit expressly states:

> The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second state of testing, by which he apparently means ***in vivo* testing in humans** and therefore **are not reasonably predictive of the succss of the claimed compounds for treating cancer in humans**. The Commissioner, as did the Board, **confuses the requirement sunder the law for obtaining a patent with the requiremens for obtaining government approval to market a particular drug for human consumption**. . .

> Our court's predecessor has determined that **proof of an alleged pharmaceutical property of a compound by statistically significant tests with standard experimental animal is sufficient to establish utility**.
>
> Similarly, the M.P.E.P. §2107.02(c) states that:
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> If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing an animal model or a combination thereof **almost invariably** will be sufficient to establish therapeutic or pharmacological utility for a compound, composition, or process. [emphasis added].

The cited reference thus clearly and unambiguously supports the efficacy of the claimed method. The Examiner has failed to offer objective basis to establish that the standard rat model described in Brana *et al.* is not reasonably correlated with the therapeutic operability/utility of the presently claimed invention. Accordingly the Examiner has failed to meet her burden and the rejection under 35 U.S.C. §112, first paragraph, (really 35 U.S.C. §101(a)/§112) should be withdrawn.

35 U.S.C. §112, second paragraph.

Claim 31 was rejected under 35 U.S.C. §112, second paragraph, as allegedly having the same scope as claim 24. Applicants traverse.

Claim 24 is directed to a kit comprising "a container containing a proton pump inhibitor (PPI); and a container containing one or more agents selected from the group consisting of a pentagastrin, and a gastrin" where the "PPI is dehydrated." Claim 31 is directed to a kit as recited in claim 24 where "said one or more agents is pentagastrin". This language further limits the earlier recitation of "one or more agents selected from the group consisting of a pentagastrin, and a gastrin". Claim 31 thus has different scope than claim 24 and the rejection under 35 U.S.C. §112, second paragraph, should be withdrawn.

Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. **Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor**.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3513.

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Respectfully submitted,

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